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EXAMINER

HILL, KEVIN KAI

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1633

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<i>Office Action Summary</i>	Application No.	Applicant(s)	
	10/533,839	KAELIN, WILLIAM G.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 November 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 16-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on November 28, 2007 is acknowledged.

Applicant has elected the invention of Group I, claim(s) 1-15, drawn to a transgenic mammal comprising a recombinant nucleic acid molecule stably integrated into the genome of said mammal, said recombinant nucleic acid molecule comprising an E2F responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, and a method for the production of said transgenic mammal.

Within Group I, Applicant has elected the following species, wherein:

- i) the transgenic mammal is a mouse,
- ii) the E2F-responsive promoter binds E2F1,
- iii) the promoter is an E2F1 promoter,
- iv) the bioluminescent protein is a luciferase, and
- v) the host cell from which to make a transgenic animal is an embryonic cell.

Upon further review and consideration of the claimed subject matter, the Examiner rejoins the "egg cell" as a species from which to make a transgenic animal.

Election of Applicant's invention(s) was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Claims 16-34 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-15 are under consideration.

Priority

This application is a 371 of PCT/US03/35282 filed on November 4, 2003. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/423,673, filed on November 4, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

If Applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

Presently, specific reference to the prior-filed applications in compliance with 37 CFR 1.78(a) is not found in the first sentence(s) of the specification following the title.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR

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1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

1. The disclosure is objected to because of the following informalities: The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP §608.01(v).

An example of such an improperly demarcated trademark is “tween”, which appears in the present specification at page 36, lines 6-7.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g. TM, ®), and accompanied by generic terminology. Applicants may identify trademarks using the “Trademark” search engine under “USPTO Search Collections” on the Internet at www.uspto.gov/web/menu/search.html.

Appropriate correction is required.

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2. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claim 7 requires the recombinant nucleic acid molecule is of human or mouse origin. While the specification discloses the E2F-responsive promoter is from a mammal, e.g. a human E2F-1 promoter (pg 2, line 14), the specification fails to disclose the mammalian origin of the entire recombinant nucleic acid molecule.

Claim 9 requires the isolation of transgenic cell types from the transgenic mammal. While the specification discloses the use of stem, germ, precursor and/or progenitor cells in the context of making transgenic cells (e.g. pg 2, lines 22-23; pg 16, line 27), the specification fails to disclose the isolation of transgenic stem, germ, precursor or progenitor cells from a transgenic mammal as required by the claim.

Applicant should amend the specification to provide proper antecedent basis for the terms while being careful not to introduce new matter into the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-9, 11 and 13 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a method of making a transgenic mammal, and said transgenic mammal. The scope of invention as claimed embraces a genetically modified human carrying in its genome or at least some of their cells recombinant genetic material, wherein the specification discloses that any cell type capable of homologous recombination may be used in the practice of the invention, including human cells (pg 17, lines 12-14). Such cells that are part of a human are non-statutory subject matter since they embrace

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the human that carries them. It is USPTO policy not to allow claims to humans (1077 O.G. 24 April 1987). See MPEP §2105.

The claims should be amended to recite "transgenic non-human mammal", support for which is found in the specification (pg 1, line 30; pg 4, line 30).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

4. Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to Claim 7, the claim is indefinite in reciting that the recombinant nucleic acid molecule is of human or murine origin. The claim literally reads as though the entire nucleic acid molecule encoding a light-generating protein must originate from human or murine. However, it would seem unlikely that either human or murine animals comprise a nucleic acid encoding a light-generating protein. Therefore, it is unclear whether the entire nucleic acid molecule of claim 1, as the claim literally recites, or only a portion of the nucleic acid molecule (e.g., the E2F-responsive promoter) is of human or murine origin. Furthermore, it is unclear what constitutes "of human or murine origin". The specification does not include any discussion of the limitation and the phrase is subject to various interpretations. For example, does the limitation require that the nucleic acid be endogenous to the human or murine genome, or might any nucleic acid isolated from a human or a mouse (e.g., a viral nucleic acid) meet the limitation? Because the meaning of the limitation "nucleic acid molecule of human or murine origin" is ambiguous and the disclosure provides no means to discern the metes and bounds of the limitation, the scope of the claim as a whole is unclear.

With respect to Claim 8, the claim is indefinite in reciting, "An isolated cell of the mammal". It is unclear whether the claimed cell is isolated from the mammal, and therefore no

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longer in the mammal, or whether the claim encompasses any cell "of" the mammal regardless of whether the cell is present in the mammal or isolated from the mammal. Although the claim states that the cell is isolated, the specification does not provide a definition of an isolated cell. Therefore, an isolated cell "of" a mammal might encompass a cell present in the mammal but not in contact with other cells (e.g., a blood cell) or a cell isolated from a source other than the mammal and implanted into the mammal (i.e., a cell of the mammal that is isolated from its native source). This rejection can be overcome by amending the claim to recite "a cell isolated from the mammal of claim 1" as contemplated, *inter alia*, at pg 31, line 24, of the specification.

With respect to Claim 9, the claim is indefinite insofar as it depends from Claim 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 6-10 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent reporter protein. At issue for the purpose of written description requirements is the description of the enormous genus of E2F-responsive promoters reasonably embraced by the claims, including an enormous genus of structurally diverse promoters that share no common core structure that clearly identifies each promoter species within the genus to possess "E2F-responsiveness", e.g. those that are not capable of binding E2F yet are claimed to be E2F-responsive.

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Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In the instant case, the specification discloses that E2F activates gene expression of a number of cell cycle-dependent genes. In tumor cells, E2F is deregulated compared to proliferating non-tumor cells (pg 5, lines 4-5). The functional activity of the E2F-responsive promoter may result in a decrease, inhibition, reduction, increase or enhancement of gene function, expression, activity or phenotype associated with the E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein (pg 11, lines 21-24). An E2F-responsive promoter includes, but is not limited to, a sub-genus of structurally distinct promoters belonging to a plurality of distinctly different genes, i.e. DHFR, thymidine kinase, DNA polymerase α , b-myb, thymidylate synthase, Rb, c-myc, Cdc2 and cyclin A (pg 12, lines 17-21; pg 13, lines 1-4) that share no common core structure or feature.

The number of promoter structures encompassed by the claims is vast and their corresponding properties, i.e. a decrease, inhibition, reduction, increase or enhancement of gene

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function, expression, activity or phenotype, as per the requirements of the claims are unknown and variable. Except for E2F-responsive promoters comprising one or more E2F canonical binding sites (pg 5, line 20; pg 13, lines 5-7), e.g. SEQ ID NO:1 (pg 12, lines 24-28), no other information is disclosed regarding what structural features would likely be associated with the desired E2F-responsive, directly or indirectly, functional properties. Furthermore, the claims reasonably embrace undisclosed promoter embodiments wherein the promoter is NOT capable of binding E2F, as evidenced by the further limitation recited in Claim 2 requiring that the E2F-responsive promoter be capable of binding E2F. The structural features that would identify a given promoter to be a member of the genus of promoters NOT capable of binding E2F yet are E2F-responsive, directly or indirectly, are not disclosed.

The specification fails to disclose sufficient identifying characteristics such as complete structure, partial structure, physical and/or chemical properties, or functional characteristics when coupled with a known or disclosed correlation between function and structure. While the specification discloses a laundry list of structurally diverse promoters, the specification fails to disclose a representative number of species which would lead one skilled in the art to conclude that the Applicant was in possession of the claimed inventive genera of promoters, directly or indirectly, responsive to E2F. Rather, those of ordinary skill in the art would recognize that the few E2F-responsive promoter species do not adequately represent the enormous genus of structurally diverse promoters that may or may not be capable of binding E2F yet respond to E2F-activity, directly or indirectly. The art does not teach a recognized or predictable correlation between a promoter's structure and its functional ability to respond to E2F activity that may result in a decrease, inhibition, reduction, increase or enhancement of gene function, expression, activity or phenotype. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of promoters that would necessarily be responsive to E2F activity, directly or indirectly, except for those that possess E2F-binding sites.

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art", "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the

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genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". MPEP §2163

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written

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description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (“definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is”).

Because the structure of the E2F-responsive promoter species within the claimed genus would be expected to vary unpredictably from the structure of the single, described subgenus, e.g. those promoters that have E2F-binding sites, the disclosed sub-genus is not a “representative number” of species within the claimed genus comprising promoters that do not have E2F-binding sites. Because the single, described subgenus is not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus, the description of the E2F-responsive promoter would not have put the Applicant in possession of common structural attributes or features shared by members of the genus that structurally distinguish the members of the genus from other materials at the time of filing. Thus, the description of the E2F-responsive promoter comprising E2F-binding sites is not sufficient to describe the claimed genus of E2F-responsive promoters that do not comprise E2F-binding sites. Accordingly, the specification does not provide a representative number of species or sufficient common structural features to show that the Applicant would have been in possession of the claimed genus as a whole at the time of filing.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all E2F-responsive promoters that achieve a result without defining the specific structures of a reasonable representation of such promoters is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, the phrase “E2F-responsive promoter” lacks written description.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

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6. Claims 1-9, 11 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a recombinant nucleic acid molecule integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, does not reasonably provide enablement for an enormous genus of transgenic animal species within the mammalian genus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is “undue” (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing an enormous genus mammalian animal species reasonably encompassing some 5,500 species (including humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007), including an enormous genus of rodents in the animal kingdom. The art teaches that there are approximately 4,000 rodent species, divided into three major groups or sub-orders, Sciuromorpha, Myomorpha and Hystricomorpha, and more than 30 families. The diversity of

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instantly claimed rodent genus reasonably encompasses, for example, squirrels, chipmunks, beavers, woodchucks, prairie dogs, hamsters, lemmings, voles, porcupines, capybaras, agoutis, chinchilla, as well as many species whose common names include the term "rat" (columbia.thefreedictionary.com/rodent).

The inventive concept in the instant application is a transgenic mouse comprising an E2F1 promoter responsive to E2F activity.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

Regarding the enormous genus of transgenic mammals, the specification discloses general methods by which a transgenic mammal may be generated (pg 12, lines 1-11; pg 16, line 23-pg 23, line 24), with specific prophetic disclosure of creating a transgenic mouse using murine embryonic stem cells or pro-nuclear injection (pg 36, Example 1; pg 37, Example 2).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

With respect to the method(s) of making a transgenic non-human animal, the art recognizes that ES cells have yet to be identified in animal species other than mouse. For example, Kuroiwa et al (Nature Genetics 36(7):775-80, 2004) teach the ES cells suitable for gene targeting are not available for species other than mouse. Moreadith et al (J. Mol. Med. 75(3): 208-216, 1997; p. 214, Summary) note that "putative" ES cells found in other animals beyond mouse lack a demonstration of the cell to give rise to germline tissue (germline transmission) or the whole animal (totipotency), a demonstration for an art-recognized property of ES cells.

In addition, the prior art and post-filing art are replete with references which indicate that ES technology is generally limited to the mouse system at present and that only "putative" ES cells exist for other species. See Rulicke et al (Experimental Physiology 85: 589-601, 2000; pg 589, col. 2, last ¶), who supports this observation, wherein Rulicke et al disclose: "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far."

Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev. 36: 607-618, 1998) teaches that:

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“The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species” (see page 608).

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of murine ES cells, other than the laboratory mouse. Mullins et al (Journal of Clinical Investigation 97(7): 1557-1560, 1996) report that: “[A]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remain a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse” (page 1558, column 2, first paragraph). Without germline transmission, breeding to homozygosity would not be possible. Accordingly, the claims appear to be only enabled for mouse.

Moreover, although Applicants contemplate in the specification methods to generate transgenic mice in whose genome a transgene may integrate, the specification fails to teach methods of generating any other transgenic mammals or other rodent species. The murine subgenus encompasses more than 1383 species of rodents, whose ES cells were yet to be discovered at the time of instant priority date and as of today, and the state of the art supports that only ES cells from laboratory mouse strains were available for use for production of transgenic mice.

The unpredictability also lies with the faulty epigenetic reprogramming in nuclei cloning. Humpherys et al (Science 293:95-97, 2001) discuss epigenetic instability in ES cells and cloned mice, and teach, “[O]nly a few percent of nuclear transfer embryos develop to term-even those clones that survive to term frequently die of respirator and circulatory problems and show increased placental and birth weights, often referred to as 'large offspring syndrome' ” (1 paragraph, page 95), “The epigenetic state of the ES cell genome was found to be extremely unstable”. “These data imply that even apparently normal cloned animals may have subtle abnormalities in gene expression” (abstract).

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The mere capability to perform gene transfer in a given species is not enabling for the claimed genus of transgenic animals because the desired phenotypes cannot be predictably achieved simply because the animal has the desired genotype. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappel et al, *Current Opinion in Biotechnology* 3: 548-553, 1992; pg 549, col. 2, ¶ 2). Wall et al (*J Dairy Sci.* 80:2213-2224, 1997) report that: "[T]ransgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, ¶1). Yanagimachi (*Mol. Cell Endocrinol.* 187:241-248, 2002) teaches that: "[C]loning efficiency as determined by the proportion of live offspring developed from all oocytes that received donor cell nuclei-is low regardless of the cell type (including, embryonic stem cells) and animal species used. In all animals except Japanese black beef cattle, the vast majority of cloned embryos perish before reaching full term" (abstract), and "thus far, cloned offspring that survived birth and reached adulthood were the exception rather than the rule (page 243, left column, emphasis added). Yanagimachi goes on to teach, "[T]his low efficiency of cloning seems to be due largely to faulty epigenetic reprogramming of donor cell nuclei after transfer into recipient oocytes. Cloned embryos with major epigenetic errors die before or soon after implantation" (abstract).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The as-filed specification fails to teach the establishment of true ES cells for use in the production of a transgenic non-human mammal other than the laboratory mouse, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic non-human mammals. Taken together, the current status of transgenic art is such that it would require undue experimentation for the ordinary artisan to generate the enormous genus of claimed transgenic non-human mammals with a requisite phenotype because the ability to make the enormous genus of claimed transgenic non-human mammals with a requisite phenotype is neither routine nor predictable unless proven by a working example. The level of one of ordinary skill in the transgenic art is considered to be high. It is not apparent as to how one skilled in the

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art reasonably correlates, without undue experimentation, between Applicant's asserted inventive mouse and the enormous genus of transgenic non-human mammals, e.g., elephants, monkeys, dogs, cats, cows, chimpanzees, capybaras, etc..., particularly in view of the foregoing reasons.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a transgenic mouse comprising a recombinant nucleic acid molecule integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the Applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the Applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

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7. Claims 1-2, 7-11 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller et al (Mol. Cell. Biol. 20(9):3316-3329, 2000), as evidenced by Muller et al (J. Biol. Chem. 274(16):11220-11228, 1999).

With respect to Claim 1, Muller et al teach a transgenic mammal comprising a recombinant nucleic acid molecule stably integrated into the genome of said mammal, said recombinant nucleic acid molecule comprising a cyclin A1 promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically GFP (pg 3317, col. 1, ¶2).

With respect to Claims 1-2, Muller et al do not teach *ipsis verbis* that the 1,444 bp (-1299 to +145) fragment of the human cyclin A1 promoter is an E2F-responsive promoter, or that it comprises E2F-binding sites. However, Muller cites the prior teaching of Muller et al (1999), wherein it is taught that this fragment does comprise at least two E2F binding sites (pg 11223, col. 2, Binding Sites). Absent evidence to the contrary, such is inherently capable of binding an E2F1 polypeptide and is an E2F-responsive promoter (specification, pg 12, line 19).

With respect to Claim 11, the promoter activity results in increased production of the bioluminescent protein (e.g. pg 3323, Figure 6). Muller et al do not teach explicitly that the increased activity is due to E2F-binding to the E2F-responsive promoter. Inherent anticipation does not require recognition in the prior art. Furthermore, "Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. In the instant case, the cyclin A1 promoter comprises E2F-binding sites, and its activity increases expression of the reporter gene. Thus, absent evidence to the contrary, the endogenous E2F1 is capable of binding to the E2F-responsive promoter to increase production of the reporter protein. The burden is shifted to the Applicant to show that the prior art cyclin A1 promoter comprising E2F-binding sites does not inherently possess the same properties as the instantly claimed promoter comprising E2F-binding sites.

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With respect to Claim 7, Muller et al teach the cyclin A1 promoter is of human origin (Muller, 1999).

With respect to Claims 8-9, Muller et al teach the isolation of germ cells from the transgenic animal (pg 3323, Figure 6; pg 3323, col. 1; pg 3324, Figure 8), as well as bone marrow cells (pg 3323, col. 2; pg 3325, Figure 9), which reasonably embraces stem cells, precursor cells and progenitor cells because those of ordinary skill in the art recognize that the bone marrow comprises said cell types (specification, pg 19, line 17).

With respect to Claim 10, Muller et al teach the transgenic mammal is a mouse.

With respect to Claims 13-15, Muller et al teach a method of making a transgenic mouse by standard techniques, the method comprising injecting recombinant DNA into the pronuclei of fertilized egg cells (pg 3317, col. 1, Generation of Transgenic Mice).

Thus, Muller et al anticipate the claims.

8. Claims 1-4, 6-8, 10-11 and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Holland (U.S. Patent 7,041,869, provisional application filed October 4, 2002), as evidenced by GenBank Accession AF516106.1, GI:21326179.

With respect to Claims 1-3, 6 and 10, Holland claims (claim 1) a transgenic mouse comprising an E2F1 promoter operably linked to luciferase. The transgene is stably integrated into the genome of the transgenic mouse (col. 4, lines 52-53). The E2F1 promoter comprises E2F binding sites (Figure 2), and thus is capable of binding E2F, absent evidence to the contrary.

With respect to Claims 4 and 7, Holland does not disclose *ipsis verbis* that the E2F1 promoter is a human E2F-1 promoter. However, the nucleotide sequence of the Holland E2F1 promoter identifies greatest identity to the human E2F-1 promoter (GenBank Accession AF516106.1, GI:21326179). Thus, absent evidence to the contrary, the recombinant nucleic acid molecule of Holland comprising the E2F-1 promoter is of human origin.

ACCESSION AF516106

VERSION AF516106.1 GI:21326179

Homo sapiens E2F transcription factor 1 (E2F1) gene, complete cds

Score = 481 bits (260), Expect = 8e-133

Identities = 263/264 (99%), Gaps = 1/264 (0%)

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Strand=Plus/Plus

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QUERY 1 CATCCGGACAAAGCCTGCGCGCGCCCCGCCCGCCATTGGCCGTACCGCCCCGCGCCGCC 60
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
SBJCT 1697 CATCCGGACAAAGCCTGCGCGCGCCCCGCCCGCCATTGGCCGTACCGCCCCGCGCCGCC 1756

QUERY 61 GCCCCATCCCGCCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGCCGCCG 120
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
SBJCT 1757 GCCCCATCCCGCCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGCCGCCG 1816

QUERY 121 TTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGCTCTTT 180
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
SBJCT 1817 TTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGCTCTTT 1876

QUERY 181 CGCGGCAAAAAGGATTTGGCGCGTAAAA-TGGCCGGGACTTTGCAGGCAGCGGCGGCCGG 239
      |||||||||||||||||||||||| ||||||||||||||||||||||||||||||||
SBJCT 1877 CGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCGGCCGG 1936

QUERY 240 GGGCGGAGCGGGATCGAGCCCTCG 263
      ||||||||||||||||||||
SBJCT 1937 GGGCGGAGCGGGATCGAGCCCTCG 1960
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With respect to Claims 8, Holland discloses cell cultures isolated from the transgenic mice (col. 11, lines 21-47).

With respect to Claim 11, Holland discloses that E2F acts at the level of transcriptional control of cellular genes that are essential for cell division (col. 5, lines 56-57), and that the cell cycle-sensitive promoter region of the E2F1 gene is used to create a cell cycle reporter, showing up-regulation upon cell cycle activity able to drive enough production of the reporter gene to allow for visualization (col. 5, lines 15-26).

With respect to Claims 13-15, Holland discloses that methods of producing transgenic mice are known in the art, including introducing the recombinant DNA into an egg cell (col. 4, lines 62-65).

Thus, Holland anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 3-7 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al (Mol. Cell. Biol. 20(9):3316-3329, 2000) in view of Neuman et al (Mol. Cell Biol. 14(10): 6607-6615, 1994; *of record in IDS), Hsiao et al (Genes & Development 8:1526-1537, 1994; *of record in IDS) and Jaenisch (Science 240: 1468-1474, 1988), as evidenced by Muller et al (J. Biol. Chem. 274(16):11220-11228, 1999) and DiLella et al (N.A.R. 16(9):4159, 1988).

Determining the scope and contents of the prior art.

Muller et al teach a transgenic mammal comprising a recombinant nucleic acid molecule stably integrated into the genome of said mammal, said recombinant nucleic acid molecule comprising a cyclin A1 promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically GFP (pg 3317, col. 1, ¶2).

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Muller et al do not teach *ipsis verbis* that the 1,444 bp (-1299 to +145) fragment of the human cyclin A1 promoter is an E2F-responsive promoter, or that it comprises E2F-binding sites. However, Muller cites the prior teaching of Muller et al (1999), wherein it is taught that this fragment does comprise at least two E2F binding sites (pg 11223, col. 2, Binding Sites). Absent evidence to the contrary, such is capable of binding an E2F1 polypeptide and is an E2F-responsive promoter (specification, pg 12, line 19).

Muller et al teach that the promoter activity results in increased production of the bioluminescent protein (e.g. pg 3323, Figure 6). Muller et al do not teach explicitly that the increased activity is due to E2F-binding to the E2F-responsive promoter. However, "Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. In the instant case, the cyclin A1 promoter comprises E2F-binding sites, and its activity increases expression of the reporter gene. Thus, absent evidence to the contrary, the endogenous E2F1 is capable of binding to the E2F-responsive promoter to increase production of the reporter protein. The burden is shifted to the Applicant to show that the prior art cyclin A1 promoter comprising E2F-binding sites does not possess the same properties as the instantly claimed promoter comprising E2F-binding sites.

Muller et al teach the isolation of germ cells from the transgenic animal (pg 3323, Figure 6; pg 3323, col. 1; pg 3324, Figure 8), as well as bone marrow cells (pg 3323, col. 2; pg 3325, Figure 9), which reasonably embraces stem cells, precursor cells and progenitor cells because those of ordinary skill in the art recognize that the bone marrow comprises said cell types (specification, pg 19, line 17).

Muller et al teach a method of making a transgenic mouse by standard techniques, the method comprising injecting recombinant DNA into the pronuclei of fertilized egg cells (pg 3317, col. 1, Generation of Transgenic Mice).

Muller et al do not teach the bioluminescent protein operably linked to the cyclin A1 promoter in the transgenic mouse is a luciferase. However, Muller et al does teach isolated

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transgenic mammalian cells comprising the cyclin A1 promoter operably linked to a bioluminescent protein, specifically luciferase (pg 3317, col. 2, Luciferase Assay).

Muller et al do not teach:

- i) the E2F-responsive promoter is an E2F-1 promoter;
- ii) the E2F-responsive promoter is a human E2F-1 promoter; and
- iii) the E2F-responsive promoter comprises SEQ ID NO:1.

However, at the time of the invention, Neuman et al taught a transgenic mammalian cell comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase (pg 6608, col. 2; pg 6609, col. 2, Results), wherein said E2F-responsive promoter is obtained from the human E2F1 promoter (pg 6608, col. 1, Genomic Cloning) that comprises a nucleic acid sequence that is 100% identical to SEQ ID NO:1 (complete sequence search results available in SCORE).

Query Match 100.0%; Score 269; DB 5; Length 362;
 Best Local Similarity 100.0%; Pred. No. 1.4e-60;
 Matches 269; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy      1  GGTACCATCCGGACAAAGCCTGCGCGCGCCCCGCCCGCCATTGGCCGTACCGCCCCGCG  60
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      20  GGTACCATCCGGACAAAGCCTGCGCGCGCCCCGCCCGCCATTGGCCGTACCGCCCCGCG  79

Qy     61  CCGCCGCCCCATCTCGCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGC 120
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     80  CCGCCGCCCCATCTCGCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGC 139

Qy    121  CGCCGTTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGC 180
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    140  CGCCGTTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGC 199

Qy    181  TCTTTCGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCG 240
      ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    200  TCTTTCGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCG 259
  
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Qy   241  GCCGGGGGCGGAGCGGGATCGAGCCCTCG  269
      |||||||||||||||||||||
Db   260  GCCGGGGGCGGAGCGGGATCGAGCCCTCG  288
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Neither Muller et al nor Neuman et al teach the E2F-responsive promoter is of murine origin. However, at the time of the invention, Hsiao et al taught a transgenic mammalian cell comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase (pg 1529, col. 2; pg 1532, Figure 5B), wherein said E2F-responsive promoter is obtained from the mouse E2F1 promoter (Abstract).

Neither Muller et al, Neuman et al nor Hsiao et al teach the method of making the transgenic mouse to comprise introducing the recombinant nucleic acid into an embryonic cell. However, at the time of the invention, Jaenisch taught that the ordinary artisan may predictably and successfully make transgenic mice by method steps such as introducing DNA into a pronucleus or embryonic stem cells (see entire paper).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells and organisms. Therefore, the level of ordinary skill in this art is high.

Neither Muller et al, Neuman et al, Hsiao et al nor Jaenisch teach a transgenic mouse comprising a luciferase reporter operably linked to a promoter of interest. However, at the time of the invention, those of ordinary skill in the art had long known that one can successfully make a transgenic mouse comprising a luciferase reporter operably linked to a promoter of interest, wherein the luciferase will predictably "report" promoter activity in the transgenic mammal, as evidenced by DiLella et al.

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Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first E2F-responsive promoter as taught by Muller et al with a second E2F-responsive promoter as taught by Neuman et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the E2F-responsive promoter as taught by Muller et al and the E2F-responsive promoter as taught by Neuman et al are both art-recognized E2F-responsive promoters, and thus equivalent in their ability to "report" E2F activity as per E2F binding to the E2F binding sites in the respective promoters. An artisan would be motivated to substitute a first E2F-responsive promoter as taught by Muller et al with a second E2F-responsive promoter as taught by Neuman et al because the E2F-responsive promoter of Neuman et al comprises a different set of transcription factor binding sites than the E2F-responsive promoter of Muller et al, and thus may yield a different tissue-specific pattern of expression than that observed for the E2F-responsive cyclin A1 promoter. Furthermore, Neuman et al teach that *in vitro* transfection experiments prohibit the determination whether E2F-1, -2, or -3 interacts with the E2F-1 promoter under physiological conditions because binding site preference differences *in vivo* between E2F family members might be obscured if they were over-produced *in vitro* (pg 6613, col. 1), thereby suggesting the production of a transgenic mammal so as to solve the problem.

It also would have been obvious to one of ordinary skill in the art to substitute a first bioluminescent reporter protein such as GFP as taught by Muller et al with a second bioluminescent reporter protein such as luciferase as taught by Neuman et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P.

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§2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art had long-recognized that bioluminescent proteins such as GFP and luciferase are functional equivalents as "reporter molecules" and readily substitutable, as successfully demonstrated by Muller et al regarding the cyclin A1 promoter operably linked to a bioluminescent protein, specifically GFP, and the cyclin A1 promoter operably linked to a bioluminescent protein, specifically luciferase. An artisan would be motivated to substitute a first bioluminescent reporter protein such as GFP with a second bioluminescent reporter protein such as luciferase because the art uses different standardized assays by which the ordinary artisan can quantify the amount of bioluminescent reporter activity in a given *in vitro* or *in vivo* system, and such is but an experimental design choice by the routineer.

It also would have been obvious to one of ordinary skill in the art to substitute a first method of making a transgenic mammal as taught by Muller et al with a second method of making a transgenic mammal as taught by Jaenisch with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first method of making a transgenic mammal as taught by Muller et al with a second method of making a transgenic mammal as taught by Jaenisch because introducing recombinant DNA into an embryonic cell and/or and egg cell, e.g. pronuclear injection, have long been recognized in the art to predictably

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succeed in producing transgenic mice, and as such the functionally equivalent methods of making transgenic mammals are but design choices for the routineer.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633